PC10015AJTJ

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Assistant Commissioner for Patents
Box PATENT APPLICATION
Washington, D.C. 20231

REQUEST FOR FILING AND
TRANSMITTAL OF UTILITY PATENT APPLICATION
PURSUANT TO 37 C.F.R. §1.51 ET SEQ

Sir:

This is a request for filing the utility patent application, transmitted herewith, of

Inventor: Murray C. Maytom and Ian H. Osterloh

Title: Method of Treating Impotence Due to Spinal Cord Injury

Enclosed are also:

☐ _____ sheets of drawing(s).

☐ An assignment of the invention to _____
(Fee for recordal of assignment, pursuant to 37 C.F.R. § 1.21(h), $40.00).

☐ A certified copy of a _____
application.

☐ A Disclosure Statement, Form FB-A820, and copy(ies) of the reference(s) cited.

XX This application is based on United States Provisional Application No. 60/075,580 filed February 23, 1998 the priority of which is hereby claimed.

XX This application is being filed without a Declaration and Power of Attorney. The undersigned attorney/agent has been authorized to file the subject application on behalf of the inventor(s).

XX All correspondence should be sent to Gregg C. Benson, Pfizer Inc., Eastern Point Road, Box 519, Groton, CT 06340.

The inventors are:

(name) Murray C. Maytom
a resident of (city, state, country) Sandwich, Kent, England
and a citizen of (country) Republic of Ireland

EXPRESS MAIL NO. EE275782474US

(name) Ian H. Osterloh
a resident of (city, state, country) Sandwich, Kent, England
and a citizen of (country) Great Britain

BASIC APPLICATION FEE: $760.00
CLAIMS FEES:

CLAIMS AS FILED

Total Claims	10	-20=	0	x $18.00	0.00
Independent Claims	2	- 3=	0	x $78.00	0.00
☐ Multiple Dependent Claim(s) fee				$260.00	0.00
Total Filing Fee					760.00

☒ Please charge Deposit Account No. 16-1445 in the amount of $760.00. Two copies of this paper are enclosed.

☒ The Commissioner is hereby authorized to charge any additional fees which may be required under 37 C.F.R. §§ 1.16 and 1.17 by the filing of this paper, or credit any overpayment, to Deposit Account No 16-1445. Two copies of this paper are enclosed.

Respectfully submitted,

Date: FEBRUARY 11, 1999

James T. Jones
Attorney for Applicant(s)
Reg. No. 30,561

Pfizer Inc.
Patent Department, Box 519
Eastern Point Road
Groton, CT 06340
(860) 441-4903

PATENT
PC10015AJTJ

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Murray C. Maytom, et al

SERIAL NO.: NOT YET ASSIGNED

FILED: HEREWITH

Examiner: Not Yet Assigned
Art Unit: Not Yet Assigned

FOR: Method of Treating Impotence Due to Spinal Cord Injury

Assistant Commissioner For Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

In the matter of the application being filed herewith, please amend the application as follows:

In the specification

Please enter the following sentence as the first paragraph in the specification, immediately following the title:

-- This application is filed claiming priority from co-pending Provisional Application No. 60/075,580 filed February 23, 1998. --

Respectfully Submitted,

Date: February 11, 1999

James T. Jones
Attorney for Applicants
Reg. No. 30,561

Pfizer Inc.
Eastern Point Road
Groton, Connecticut 06340
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METHOD OF TREATING IMPOTENCE DUE TO SPINAL CORD INJURY

Field Of The Invention

This invention relates to a method of treating sexual dysfunction due to spinal cord injury (SCI) comprising administering an effective amount of a compound of formula I as defined below, including pharmaceutically acceptable salts thereof.

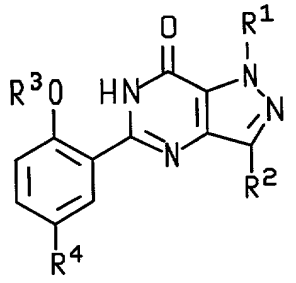
Background Of The Invention

Impotence is the inability to obtain and/or sustain an erection sufficient for penetration of the vagina and/or intercourse. Thus, impotence is also referred to as "erectile insufficiency" or "erectile dysfunction". It has been estimated that 10-12 million American men between the ages of 18 and 75 suffer from chronic impotence, with the great majority being over age 55.

The penis normally becomes erect when certain tissues, in particular the corpora cavernosa in the central portion of the penis, become engorged with blood, thereby causing them to become rigid, causing an erection. Impotence can result from psychologic disturbances (psychogenic), from physiologic abnormalities (organic) or from a combination of both. Thus, in some males erectile dysfunction may be due to anxiety or depression, with no apparent somatic or organic impairment. In other cases, erectile dysfunction is associated with atherosclerosis of the arteries supplying blood to the penis. In still other cases, the dysfunction may be due to venous leakage or abnormal drainage in which there is leakage from veins in the penis such that sufficient pressure for an erection can be neither obtained nor maintained. In still other cases, the dysfunction is associated with a neuropathy or due to nerve damage arising from, for example, surgery or a pelvic injury. Typically, multiple factors are responsible for impotence.

Summary Of The Invention

This invention provides a method of treating sexual dysfunction in an animal with an injured spinal cord, comprising administering to an animal, particularly a human, in need of such treatment an effective amount of a compound of formula (I):



(I)

wherein:

R^1 is H; C_1-C_3 alkyl; C_1-C_3 perfluoroalkyl; or C_3-C_5 cycloalkyl;

R^2 is H; C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_3 perfluoroalkyl; or C_3-C_6 cycloalkyl;

R^3 is C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_6 perfluoroalkyl; C_3-C_5 cycloalkyl; C_3-C_6 alkenyl; or C_3-C_6 alkynyl;

R^4 is C_1-C_4 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkanoyl optionally substituted with NR^5R^6; (hydroxy)C_2-C_4 alkyl optionally substituted with NR^5R^6; (C_2-C_3 alkoxy)C_1-C_2 alkyl optionally substituted with OH or NR^5R^6; $CONR^5R^6$; CO_2R^7; halo; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl;

R^5 and R^6 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-N(R^{11})-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH;

R^7 is H or C_1-C_4 alkyl;

R^8 is C_1-C_3 alkyl optionally substituted with NR^5R^6;

R^9 and R^{10} together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino or 4-N(R^{12})-piperazinyl group wherein said group is optionally substituted with C_1-C_4 alkyl, C_1-C_3 alkoxy, $NR^{13}R^{14}$ or $CONR^{13}R^{14}$;

R^{11} is H; C_1-C_3 alkyl optionally substituted with phenyl; (hydroxy)C_2-C_3 alkyl; or C_1-C_4 alkanoyl;

R^{12} is H; C_1-C_6 alkyl; (C_1-C_3 alkoxy)C_2-C_6 alkyl; (hydroxy)C_2-C_6 alkyl; ($R^{13}R^{14}N$)C_2-C_6 alkyl; ($R^{13}R^{14}NOC$)C_1-C_6 alkyl; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$; or $C(NH)NR^{13}R^{14}$; and

R^{13} and R^{14} are each independently H; C_1-C_4 alkyl; (C_1-C_3 alkoxy)C_2-C_4 alkyl; or (hydroxy)C_2-C_4 alkyl;

or a pharmaceutically acceptable salt thereof;

or a pharmaceutical composition containing either entity.

The above compounds are disclosed, inter alia, in US patents 5,250,534, 5,272,147 and 5,426,107, all herein incorporated by reference, and in WO 94/28902.

Types of sexual dysfunction due to spinal cord injury which are treatable by means of this invention include male erectile dysfunction and female sexual dysfunction such as orgasmic dysfunction and arousal disorders.

"Sexual dysfunction in an animal with an injured spinal cord" means sexual dysfunction in an animal due to the trauma and/or nerve damage which accompanies a physical spinal cord injury or nerve damage resulting from organic disease. In this type of injury the cortical components of sexual arousal (for example visual sexual stimulation) are disassociated from the localized reflexogenic component of the arousal process. There are, of course, varying degrees of spinal cord injury. The average male patient suffers nerve damage sufficient to prevent the patient from being able to obtain and/or sustain an erection sufficient for intercourse, yet the patient still exhibits a reflexogenic erectile response. It is considered unique to administer an oral drug that only in the presence of tactile genital stimulation (as occurs in sexual foreplay) has the ability to prolong and enhance the normal reflexogenic response in this SCI patient population. The use of a compound according to the present invention can restore erectile function to the point that an SCI patient can sustain an erection sufficient for intercourse.

A subset of spinal cord injured patients includes male patients who have essentially no residual erectile function following the injury. Such a patient can be defined as one who exhibits no apparent erectile response, indicating no reflexogenic erectile response to local stimulation, usually penile vibratory stimulation (PVS), and no erections induced by other means (e.g., visual stimulation). It has been determined that use of a compound in accordance with this invention can restore erectile function sufficient for intercourse in a substantial proportion of this SCI patient population. It is truly surprising that erectile function can be restored in a patient who has sustained a SCI to the extent that, in the absence of treatment with a compound of formula (I), local stimulation produces no apparent erectile response.

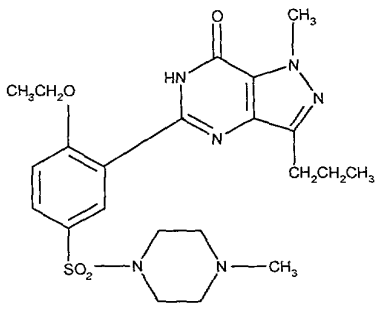
Detailed Description

Reference to a compound of formula I, both in this disclosure and the appendant claims, shall at all times be understood to include all active forms of such compounds, including the free form thereof (e.g., the free acid or base form) and also all pharmaceutically acceptable salts, prodrugs, polymorphs, hydrates, solvates, stereoisomers (e.g. diastereomers and enantiomers), and so forth. Active metabolites of such compounds are also included.

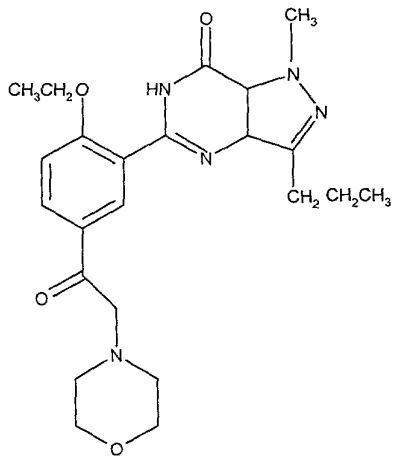
Preferred compounds of formula (I) include those which can be taken as required, as compared with needing to be taken chronically. Such preferred compounds include those which improve the sexual response such that the patient responds to sexual (e.g., visual and/or tactile) stimulation, as opposed to compounds which act by causing an erection in the absence of sexual stimulation.

Additional preferred compounds include those which are "fast acting", meaning that the time taken from administration to the point at which the sexual response is improved is less than about two hours, preferably less than about one hour, more preferably on the order of a half hour or less, and even more preferably within 10 or 15 minutes.

Preferred compounds (which are cGMP PDE_v inhibitors) include sildenafil, 5-[2-ethoxy-5-(4-methyl-l-piperazinylsulphonyl)-phenyl]-l-methyl-3-n-propyl-l,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, which has the structure:



and pharmaceutically acceptable salts thereof, and the compound having the structure:



and pharmaceutically acceptable salts thereof. The first compound, sildenafil, is disclosed in US patent 5,250,534, herein incorporated by reference. The second compound is disclosed, for example, in US patents 5,272,147 and 5,426,107, both incorporated herein by reference.

A preferred pharmaceutically acceptable salt of sildenafil for use in this invention is the citrate salt, disclosed in co-pending U. S. provisional Application No. 60/027,690 filed October 8, 1996 and incorporated herein by reference.

Other preferred compounds of formula (I) include those compounds selected from:

5-(5-morpholinoacetyl-2-n-propoxyphenyl)-l-methyl-3-n-propyl-l,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-allyloxy-5-(4-methyl-l-piperazinylsulphonyl)-phenyl]-l-methyl-3-n-propyl-l,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-propyl)-l-piperazinyl-sulphonyl]phenyl}-l-methyl-3-n-propyl-l,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-hydroxyethyl)-l-piperazinyl-sulphonyl]phenyl}-l-methyl-3-n-propyl-l,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{5-[4-(2-hydroxyethyl)-l-piperazinylsulphonyl]-2-n-propoxyphenyl}-l-methyl-3-n-propyl-l,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-l-piperazinylcarbonyl)-phenyl]-l-methyl-3-n-propyl-l,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and

5-[2-ethoxy-5-(l-methyl-2-imidazolyl)phenyl]-l-methyl-3-n-propyl-l,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

The above compounds are disclosed in the aforementioned US patents 5,250,534, 5,272,147 and 5,426,107.

A compound of formula I will generally be administered via any of the known routes of administration such as oral, parenteral via local injection intracavernosally or intraurethrally, or transdermal as by applying the active component in a gel or other such formulation topically to the penis. Oral administration is preferred. The compound can be formulated as known in the art, usually together with a pharmaceutically acceptable carrier or diluent, for example as a tablet, capsule, lozenge, troche, elixir, solution, or suspension for oral administration, in a suitable injectable vehicle for parenteral administration, or as a lotion, ointment or cream for topical application.

The exact dose administered will, of course, differ depending on the specific compound of formula I prescribed, on the subject being treated, on the severity of the organic dysfunction, on the manner of administration and on the judgment of the prescribing physician. Thus, because of patient-to-patient variability, the dosages given below are a guideline and the physician may adjust doses of the compounds to achieve the treatment that the physician considers appropriate for the patient. In considering the degree of treatment desired, the physician must balance a variety of factors such as the age and sex of the patient and the presence of other diseases or conditions (e.g., cardiovascular disease). In general, the compound of formula I will be administered in a range of from 10 to 200 mg, preferably 25 to 100 mg, taken as required not more than once daily. Usually, the compound will be taken on demand, anywhere from a few minutes up to several hours prior to intercourse. As previously noted, a compound of formula I can be administered in any conventional oral, parenteral, rectal or transdermal dosage form, usually also together with a pharmaceutically acceptable carrier or diluent.

For oral administration a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants such as starch and preferably potato or tapioca starch and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous

suspensions and/or elixirs are desired for oral administration, a compound of formula I can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts. Such aqueous solutions may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art.

For purposes of transdermal (e.g.,topical) administration, dilute sterile, aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are prepared.

Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples of methods of preparing pharmaceutical compositions, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

As an example of the invention, a study was conducted which had a double-blind, randomised, placebo-controlled, single dose, two-way crossover design. After a screening period in which only patients with at least a grade 2 (i.e., hard, but not hard enough for vaginal penetration) reflexogenic erectile response to a vibrator were included, fasted patients were randomly allocated to receive a single oral dose of 50 mg of sildenafil or placebo, administered an double-blind fashion in a private room; a washout period of 3 days was used between the crossover periods.

Twenty-seven male patients (mean age 32.9 years, range 21-49 years) with erectile dysfunction solely attributable to a spinal cord injury (cord level range T6-L4/5) were studied. One patient did not complete the study.

Reflexogenic erections were stimulated by applying a vibrator to the shaft and glans of the penis at set times: T=0 (pre-dose), and at T=0.5 hour, T=1 hour, and T=1.5 hours. Efficacy was evaluated by RigiScan® penile plethysmography recordings.

Twenty six patients were evaluable. No patients discontinued treatment due to adverse events. The results of the RigiScan® assessments (Stage I) and the primary efficacy analysis question** answered at the end of the 28-day treatment period (Stage II) are shown in Tables A and B immediately below:

STAGE I: single-dose, two-way crossover study	
RigiScan® recordings (n=26)	
	No. patients (%) with penile BASE rigidity >60%
SILDENAFIL	17/26 (65%)*
PLACEBO	2/26 (8%)

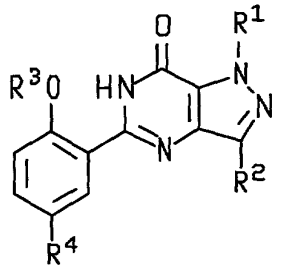
* significantly different from placebo, $p<0.01$

STAGE II: 28-day, parallel-group study		
†Has the treatment you have been taking over the last 4 weeks improved your erections?		
	YES	NO
SILDENAFIL (n=12)	9/12 (75%)**	3/12 (25%)
PLACEBO (n=14)	1/14 (7.1%)	13/14 (92.9%)

** significantly different from placebo, $p<0.01$

What is claimed is:

1. A method of treating sexual dysfunction in an animal with an injured spinal cord, comprising administering to an animal in need of such treatment an effective amount of a compound of formula (I):



(I)

wherein:

R^1 is H; C_1-C_3 alkyl; C_1-C_3 perfluoroalkyl; or C_3-C_5 cycloalkyl;

R^2 is H; C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_3 perfluoroalkyl; or C_3-C_6 cycloalkyl;

R^3 is C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_6 perfluoroalkyl; C_3-C_5 cycloalkyl; C_3-C_6 alkenyl; or C_3-C_6 alkynyl;

R^4 is C_1-C_4 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkanoyl optionally substituted with NR^5R^6; (hydroxy)C_2-C_4 alkyl optionally substituted with NR^5R^6; (C_2-C_3 alkoxy)C_1-C_2 alkyl optionally substituted with OH or NR^5R^6; $CONR^5R^6$; CO_2R^7; halo; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl;

R^5 and R^6 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-N(R^{11})-

piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH;

R^7 is H or C_1-C_4 alkyl;

R^8 is C_1-C_3 alkyl optionally substituted with NR^5R^6;

R^9 and R^{10} together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino or 4-N(R^{12})-piperazinyl group wherein said group is optionally substituted with C_1-C_4 alkyl, C_1-C_3 alkoxy, $NR^{13}R^{14}$ or $CONR^{13}R^{14}$;

R^{11} is H; C_1-C_3 alkyl optionally substituted with phenyl; (hydroxy)C_2-C_3 alkyl; or C_1-C_4 alkanoyl;

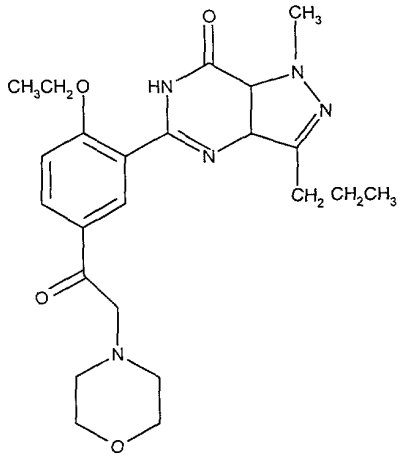
R^{12} is H; C_1-C_6 alkyl; (C_1-C_3 alkoxy)C_2-C_6 alkyl; (hydroxy)C_2-C_6 alkyl; ($R^{13}R^{14}$N)C_2-C_6 alkyl; ($R^{13}R^{14}$NOC)C_1-C_6 alkyl; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$; or $C(NH)NR^{13}R^{14}$; and

R^{13} and R^{14} are each independently H; C_1-C_4 alkyl; (C_1-C_3 alkoxy)C_2-C_4 alkyl; or (hydroxy)C_2-C_4 alkyl;

or a pharmaceutically acceptable salt thereof;

or a pharmaceutical composition containing either entity.

2. A method as defined in claim 1, wherein said compound is selected from sildenafil, and pharmaceutically acceptable salts thereof, and the compound having the structure:



and pharmaceutically acceptable salts thereof.

3. A method as defined in claim 1, wherein said compound is sildenafil or a pharmaceutically acceptable salt thereof.

4. A method as defined in claim 3, wherein said pharmaceutically acceptable salt is the citrate.

5. A method of treating sexual dysfunction in an animal with an injured spinal cord, comprising administering to an animal in need of such treatment an effective amount of sildenafil, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

6. A method as defined in claim 5, wherein said pharmaceutically acceptable salt is the citrate.

7. A method as defined in claim 1, wherein said animal is male and exhibits essentially no residual erectile function.

8. A method as defined in claim 5, wherein said animal is male and exhibits essentially no residual erectile function.

9. A method as defined in claim 1, wherein said animal is human.

10. A method as defined in claim 5, wherein said animal is human.

ABSTRACT

A class of cGMP PDE inhibitors, including sidenafil and pharmaceutically acceptable salts thereof, which can be used to treat sexual dysfunction in male and female animals, especially humans, with a spinal cord injury. The invention can be used to treat sexual dysfunction in male animals that exhibit essentially no residual penile function.

PTO/SB/01(12/97)
Approved for use through 09/30/2000. OMB 0651-0032
Patent and Trademark Office: U.S DEPARTMENT OF COMMERCE

Please type a plus sign (+) inside this box → [+]

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☒ Declaration submitted with Initial Filing

☐ Declaration Submitted after Initial Filing (surcharge 37 CFR 1.16 (e)) required)

Attorney Docket Number	PC10015AJTJ
First Named Inventor	Murray C. Maytom
COMPLETE IF KNOWN	
Application Number	To Be Assigned
Filing Date	Herewith
Group Art Unit	To Be Assigned
Examiner Name	To Be Assigned

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Method of Treating Impotence Due to Spinal Cord Injury

(Title of the Invention)

the specification of which
☒ is attached hereto
OR
☐ was filed on (MM/DD/YYYY) [ ] as United States Application Number or PCT International

Application Number [ ] and was amended on (MM/DD/YYYY) [ ] (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below:

Application Number(s)	Filing Date (MM/DD/YYYY)	
60/075,580	2-23-98	☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B sheet attached hereto.

EXPRESS MAIL NO. EE377282474US [Page 1 of 3]

PTO/SB/01 (12/97)
Approved for use through 09/30/2000 OMB 0651-0032
Patent and Trademark Office: U.S DEPARTMENT OF COMMERCE

Please type a plus sign (+) inside this box → [+]

DECLARATION ---- Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 U.S.C. 1.56, which became available between the filing date of the prior application and the national or PCT International filing date of this application.

U.S. Parent Application Number or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT International application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: ☐ Customer Number or ☒ Registered practioner(s) name/registation number listed below

[ ] → Place Customer Number Bar Code Label here

Name	Registration Number	Name	Registration Number
Peter C. Richardson	27,526	Raymond W. Augustin	28,588
Allen J. Spiegel	25,749	Paul H. Ginsburg	28,718
Aaron Passman	26,783	Mark Dryer	28,775
J. Trevor Lumb	28,567	Elizabeth O. Slade	29,011
James T. Jones	30,561	Lawrence C. Akers	28,587
Gregg C. Benson	30,997	John L. LaPierre	29,185
Robert F. Sheyka	31,304	A. Dean Olson	31,185
Grover F. Fuller Jr.	31,760	Howard R. Jaeger	31,376
Karen DeBenedictis	32,977	Mervin E. Brokke	32,723
Phillip C. Strassburger	34,258	Valerie M. Fedowich	33,688
Lorraine B. Ling	35,251	Bryan C. Zielinski	34,462
Garth Butterfield	36,997	Robert T. Ronau	36,257
Carl J. Goddard	39,203	B. Timothy Creagan	39,156
Raymond M. Speer	26,810	Alan L. Koller	37,371
Jennifer A. Kispert	40,049	Jolene W. Appleman	35,428
Martha A. Gammill	31,820	Kristina L. Konstas	37,864
Kenneth B. Rubin	36,259	Gregory P. Raymer	36,647

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☐ Customer Number or Bar Code Label [ ] OR ☒ Correspondence address below

Name	Gregg C. Benson				
Address	Pfizer Inc.				
Address	Eastern Point Road				
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Country	USA	**Telephone**	860-441-4903	**Fax**	860-441-5221

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
Murray C.	Maytom

Inventor's Signature						**Date**	
Residence: City	Sandwich	**State**	Kent`	**Country**	England	**Citizenship**	Republic of Ireland
Post Office Address	Pfizer Limited						
Post Office Address	Pfizer Limited						
City	Sandwich	**State**	Kent	**Zip**	CT13 9NJ	**Country**	England

☒ Additional inventors are being named on the x a supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto.

PTO/SB/02A(3/97)
Approved for use through 09/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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DECLARATION	ADDITIONAL INVENTOR(S) Supplemental Sheet

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
Ian H.				Osterloh			
Inventor's Signature						**Date**	
Residence: City	Sandwich	**State**	Kent	**Country**	England	**Citizenship**	Great Britain
Post Office Address	Pfizer Limited						
Post Office Address	Pfizer Limited						
City	Sandwich	**State**	Kent	**Zip**	CT13 9NJ	**Country**	England

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
Post Office Address							
City		**State**		**Zip**		**Country**	

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
Post Office Address							
City		**State**		**Zip**		**Country**	

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
Post Office Address							
City		**State**		**Zip**		**Country**	